REMARKS

Claims 26, 42, 46, and 47 are pending in the application, claims 27, 39, and 40 having been canceled by the present amendment. Claims 41, 43, 44, and 45 are withdrawn from consideration at this time as a result of a species election, and may be examined in this application pending the outcome of the examination of the elected species.

The amendment of claim 26 and new claim 27 are supported by disclosure at page 9, lines 18-29, and page 13, lines 1-9, of the specification. New claim 27 is further supported by disclosure at page 5, lines 18-19, of the specification.

Informalities in the disclosure have been corrected as follows. The specification has been amended to clarify that HAAH polypeptide refers to the amino acid sequence of SEQ ID NO:2 and HAAH cDNA refers to the nucleotide sequence of SEQ ID NO3. The specification has also been amended to insert a reference to a sequence (SEQ ID NO:2) on page 6, line 16.

The claims have further been amended to insert sequence identifiers.

With respect to the Declaration/ Power of Attorney, co-inventor, Dr. Carlson, has initialed and dated the correction of his home address. An initialed/dated copy of the Combined Declaration and Power of Attorney document is submitted herewith.

No new matter has been added.

I. Rejections under 35 U.S.C. § 112, second paragraph

Claims 26, 27, 39, 40, and 42 were rejected for indefiniteness for recitation of the claim terms "HAAH" and "NOTCH". The Examiner states:

> The use of laboratory designations only to identify a particular protein renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to incorporate a sequence identifier would overcome this rejection.

With respect to "HAAH", the claims have been amended to include the full name of the enzyme "human aspartyl (asparaginyl) beta-hydroxylase" as well as a sequence identifier "SEQ ID NO:2. With respect to "NOTCH", Applicants submit that this claim term is not simply a laboratory designation, but an art-recognized term that identifies a distinct family of proteins. One of skilled in the art would immediately understand the metes and bounds of the claim term "NOTCH". The family

of NOTCH gene products and corresponding nomenclature has been known in the art for nearly 20 years. Moreover, a sequence identifier for EGF repeat sequences (SEQ ID NO:4), a distinguishing characteristic of NOTCH proteins, has been added to the claim to more clearly define the hydroxylation target sequence of the HAAH enzyme.

Withdrawal of this rejection is therefore requested.

II. Rejections under 35 U.S.C. § 112, first paragraph

Claims 26, 27, 39, 40, and 42 were rejected for overbreadth.

With respect to "HAAH", the Examiner states:

> the applicant was not in possessionof the claimed geneus because a description of only one memner of this genus is not representative of the variants of the genus and is therefore insufficient to support the claime to a genus of HAAH proteins.

The claims have been amended to insert sequence identifier SEQ ID NO:2 to define the amino acid sequence of HAAH.

Regarding NOTCH, the Examiner further states:

> With regard to the NOTCH polypeptide, the specification does not provide a definition of what constitutes said NOTCH protein but suggests that examples of NOTCH proteins contain the motif SEQ ID NO:4. However, this embodiment is not present in claims 26, 27, 40 or 42, and is therefore non-limiting to the scope of structures encompassed by claims 26, 27, 40, or 42.

The claims have been amended to insert sequence identifier, SEQ ID NO:4, to define the EGF repeat sequences of NOTCH and to define the target sequences of HAAH hydroxylation.

Applicants submit that the scope of the amended claims is commensurate with the teachings of the specification and therefore request withdrawal of this amendment.

III. Rejections under 35 U.S.C. § 102

Claims 26, 27, and 39 were rejected for anticipation by DeWys et al. as evidenced by Hanauske-Abel et al., the Sigma catalog, Lavaissiere et al., and Kelley et al. In the paragraph spanning pages 6-7 of Paper No. 11, the Examiner states:

> It is reasonable to conclude that the administration of L-mimosine, which is known to inhibit tumor growth in a mammal (De Wys et al. inherently inhibits the HAAH hydroxylation of the EGF repeats in a NOTCH polypeptide.

Claims 27 and 39 were canceled. Claim 26 was amended to require a liver cell that overexpresses an endogenous HAAH polypeptide (having the amino acid sequence of SEQ ID NO:2)

DeWys describes the Walker 256 carcinoma system (mammary gland derived tumor cells), Lewis lung carcinoma, and L1210 leukemia system. This reference fails to describe HAAH-overexpressing liver cells. Therefore, claim 26 is not anticipated by DeWys et al.

IV. Rejections under 35 U.S.C. § 103

Claims 26, 27, 39, 40, 42, and 43 were rejected for obviousness ov er DeWys et al. as evidenced by Hanauske-Abel et al., the Sigma catalog, Lavaissiere et al., and Kelley et al. In support of the rejection, the Examiner states:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat hepatocellular carcinoma by the administration of L-mimosine or other hydroxypyridone compounds. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of DeWys on the toxicity of mimosine against rapidly growing cell systems, the teachings of Hanuske-Abel et al. and the [S]igma Catalog on theinhibition of prolyl hydroxylation by L-mimosine and the teachings of Lavaissiere et al. on the elevated level of hydroxylase activity in hepatocellular carcinoma tissues. One of skill in the art would have concluded that the toxicity of L-mimosine against rapidly growing [c]ell systems, such as cancer cells, would be attributed to its inhibition of prolyl hydroxylation, and that L-mimosine would induce a toxic effect on the hepatocellular carcinoma cells due to the inhibition of elevated prolyl hydroxylation caused by the over expression of HAAH. (emphasis added)

As a preliminary matter, the claims have been amended to require inhibition of hydroxylation of an aspartic acid or an asparagine residue in an EGF-like domain (SEQ ID NO:2) by a human aspartyl (asparaginyl) beta-hydroxylase (HAAH). The specificicity of the hydroxylase required by the amended claims is beta-hydroxylation of an aspartic acid or asparagine residue, rather than prolyl hydroxylation, i.e., hydroxylation of a proline residue.

As was discussed above, DeWys et al. describes inhibition of the growth of three discrete tumor types by administration of mimosine. These researchers describe mimosine as a "tyrosine inhibitor" (abstract) and further state,

> Mimosine appears to act as an amino acid analog and thus may be classed with L-asparaginase, the glutamic acid antagonists, 2-thienylalanine, and desoxypyridoxine, and other agents affecting amino acid metabolism. (citations omitted; page 48, col. 1, paragraph 1, of DeWys et al.)

This reference fails to describe HAAH hydroxylation or any hydroxylation inhibitory activity of mimosine.

> With respect to Hanauske-Abel et al. and the Sigma catalog, the Examiner states:
>
> Hanauske-Abel et al. disclose that human prolyl 4-hydroxylase is inhibited by hydroxypyridone compounds (column 4, lines 7-9) The Sigma catalog identifies L-mimosine as a hydroxy pyridone compound.

Hanauske-Abel et al. describes fibrotic or fibroproliferative disorder, e.g., hepatic fibrosis, liver cirrhosis, pulmonary fibrosis, restenosis, renal fibrosis, myclofibrosis, scleroderma, neonatal liver fibrosis, post-burn scarring, eye surgery scarring, or keloids. This reference fails to describe a tumor of any sort, much less a tumor characterized by overexpression of HAAH and methods of inhibiting growth of such a tumor by inhibiting HAAH hydroxylation activity.

Moreover, the enzymes and substrates described by Hanauske-Abel et al. are completely different from the enzyme and substrate required by the claims. The passage in the Hanauske-Abel et al. reference to which the Examiner referred describes "inhibition of purified human prolyl 4-hydroxylase relative to uninhibited enzyme activity, by several representative hydroxypyridone compounds" in a cell-free system. The enzyme, human prolyl 4-hydroxylase, catalyzes hydroxylation of proline residues in collagen. In contrast, the claims require inhibition of hydroxylation of an aspartic acid or an asparagine residue by a human of aspartyl(asparaginyl)-beta hydroxylase. The enzyme required by the claims catalyzes posttranslational hydroxylation of beta carbons of specific aspartyl and asparaginyl residues in EGF repeat domains of certain proteins such as NOTCH proteins.

The Sigma catalog simply states the chemical formula for L-mimosine (β-[N-(3-Hydroxy-4-pyridone)]α-aminopropionic acid) indicating that it is a "comparatively rare α-amino acid reported to produce alopecia in humans. May also cause cataracts. A pyridoxal antagonist that inhibits growth and protein synthesis in microorganisms." (citations omitted). This reference fails to describe inhibition of any enzyme activity, much less inhibition of hydroxylation of an aspartic acid or an asparagine residue in an EGF repeat domain (SEQ ID NO:4) by a human of aspartyl(asparaginyl)-beta hydroxylase. Thus, the combination of DeWys et al., Hanauske-Abel et al., and the Sigma catalog do not suggest inhibition of HAAH-mediated hydroxylation of EGF domains in liver tumor cells that overexpress HAAH.

Lavaissiere et al. describe HAAH overexpression in hepatocellular carcinoma and cholangiocarcinoma, and Kelley et al. describe a consensus sequence for EGF repeats in NOTCH proteins. There is explicit or implicit suggestion to combine Lavaissiere et al. or Kelley et al. with any of the references discussed above (DeWys et al., Hanauske-Abel et al., or the Sigma catalog). Although DeWys et al., Hanauske-Abel et al., and the Sigma catalog describe mimosine, they either

fail to describe hydroxylation (DeWys et al., Sigma catalog) or describe inhibition of an enzymatic activity that differs from the beta-hydroxylation activity of HAAH (Hanauske-Abel et al.) Thus, a *prima facie* case of obviousness has not been established.

Even if the references were properly combined, the combination fails to suggest the invention as now claimed. If anything, the cited combination of references might suggest that it would be obvious to to the inhibit "elevated prolyl hydroxylation caused by the over expression of HAAH", as stated by the Examiner. However, the claims are drawn to methods of inhibiting human aspartyl (asparaginyl) beta-hydroxylase, a completely different enzyme with a completely different specificity. None of the cited references suggest inhibiting the HAAH enzyme nor do they provide any evidence that compounds that inhibit other hydroxylase enzymes would inhibit the specific hydroxylase enzyme required by the claims in the cells specified by the claims. Therefore, claim 26 and those claims that depend from claim 26 are nonobvious over the cited combination of references. Withdrawal of this rejection is respectfully requested.

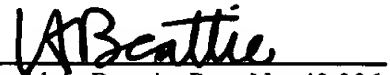
CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

A petition for extension of time and a check in the amount of $ 930.00 is enclosed to cover the petition fee for a three month extension of time pursuant to 37 C.F.R. § 1.17(a)(3). The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21486-032DIV4.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



Ingrid A. Beattie, Reg. No. 42,306
Attorney for Applicant
MINTZ, LEVIN, COHN, FERRIS
GLOVSKY and POPEO, P.C.
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000

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